REMARKS

In view of the amendments and remarks presented herein, the Applicants request withdrawal of the rejections and favorable reconsideration of the claims.

Applicants thank Examiner Siew for the two telephone conferences on April 9, 2004 during which the claimed subject matter, the technique of sequencing by hybridization and the above amendment to claim 47 were discussed in view of the present rejections. Applicants believe that the above amendment 47 and the following remarks now place the case in condition for allowance.

I. Status of the Claims

Claims 47-121 are pending in the instant application. Claims 102-121 have been withdrawn as directed to non-elected subject matter. Claims 47-101 stand variously rejected under 35 U.S.C. §102(b) and/or under 35 U.S.C. §103(a), and further under the judicially created doctrine of obviousness-type double patenting. Applicants respectfully traverse the rejections and request reconsideration in light of the above amendments and the following remarks.

II. Rejection under obviousness-type double patenting should be held in abeyance.

Claims 47-97, 99 and 101 were rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,401,267. Claims 98 and 100 were rejected under the same doctrine over claims 1-40 of U.S. Patent No. 6,401,267 in view of Duck et al. (U.S. Patent No. 4,876,187).

Applicants attach hereto a terminal disclaimer over U.S. Patent No. 6,401,267 which obviates the rejection.

III. Description of Sequencing by Hybridization.

As discussed with the Examiner on April 9, 2004, the basic sequencing technology being discussed in the present application is sequencing by hybridization (SBH). This technique determines the sequence of a target nucleic acid by reconstructing a sequence using information derived from overlapping smaller oligomers that are constituents of the target nucleic acid (Strezoska *et al. Proc. Natl. Acad. Sci. USA*, 88:10089-10093, 1991; page 10089 second paragraph; Drmanac *et al. Electrophoresis* 13:566-573, 1992, see abstract and second column of p566; Southern WO 89/10977; Khrapko *et al.*, 1991 (all previously supplied). Thus, as early as 1992, it was recognized that fragments of up to 10kb can be ***sequenced*** using 50,000 to 100 000 probes using various algorithms (Drmanac *et al. Electrophoresis* 13:566-573, 1992, see abstract and second column of p566). Prior to the present invention, there were two types of SBH techniques, SBH 1 (Drmanac *et al. Electrophoresis* 13:566-573, 1992; Southern *et al.*, Genomics, 13:1008-1017, 1992) and SBH-2 (See Southern WO 89/10977; Khrapko *et al.*, 1991). These techniques were discussed further in the previous response.

The present invention is directed to a new type of sequencing by hybridization termed ***SBH format 3***, which in contrast to the prior art methods uses hybridization with ***two sets of oligonucleotides*** of known sequence that can be used to interrogate the unknown target nucleic acid whose sequence is to be determined by reconstructing the sequence from overlapping oligonucleotides. Claim 47 has been clarified to expressly recite this in step (e). Support for the amendment is found throughout the specification, see e.g., page 8, lines 4-15). This amendment is presented purely by way of clarification and is not necessitated to distinguish any of the art cited by the Examiner because the original claim 47 as filed encompassed and described the same steps of the technique as being claimed by the present, clarified claim language. Claim 71 is cancelled.

IV. Rejection under 35 U.S.C. §102(b) should be withdrawn

Claims 47-55, 57, 59-75, 79-82, 84-91, 93-96 and 101 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Landegren et al. (U.S. Patent No. 4,988,617).

The methods of the present invention are entirely distinguishable from the disclosure of Landegren *et al.*, because Landegren does not involve determining the sequence of a target nucleic acid, but is instead directed only to assessing whether or not a point mutation may be present in a given sequence. As discussed above, the technique of SBH in general involves compiling the actual nucleotide sequence of a given target nucleic acid, and not just detecting whether or not the target sequence contains a mismatch. Step (d) involves compiling the sequence of the target nucleic acid connecting the nucleotide sequences of the detected labeled oligonucleotide probe(s) with the nucleotide sequences of their respective joined immobilized oligonucleotide probe(s) and step (e) expressly recites that the sequence of the nucleic acid is reconstructed from overlapping oligonucleotides of step (d).

The compilation of the nucleic acid sequence is not disclosed or suggested by the Landegren document. Instead, Landegren only teaches a "Method of Detecting a Change in Nucleic Acids," in which a target sequence is interrogated with the knowledge of the "known normal sequence" of that target and the knowledge of the "known possible mutation of at least one target nucleotide position" (Col. 2, lines 34-40). In performing this interrogation, the Landegren method requires that one of the two probes used (termed the "target probe" by Landegren) "is complementary to and therefore capable of base pairing with either the normal or abnormal nucleotide at the corresponding target nucleotide position" (Col. 2 lines 48-50). The linking agent will only link the two probes "when the target nucleotide is correctly base paired . . . and if not correctly based paired the probes are incapable of being covalently joined under such conditions." The presence or absence of the linking is used as the measure of the presence or absence of the ***known mutation*** in the interrogated nucleic acid. Thus, Landegren only is directed to detecting ***the presence or absence of a known*** point mutation in a target nucleic acid and does not provide a method of sequencing the target nucleic acid sequence. Further Landegren specifically requires that the

test substance (*i.e.*, the target nucleic acid whose sequence is being interrogated) is separated or melted away from the annealed probes (see Col. 3, lines 1-21, and especially, line 17-18). This step is not required in the methods of the present invention.

As the Landegren document fails to describe a method of sequencing a target nucleic acid from overlapping sequences (i.e., a method of SBH), and further because the Landegren reference requires that in order to properly detect point mutations, the method must comprise a step in which the ligated probe products are separated from the target sequence before sequence analysis can be performed, Landegren does not anticipate claim 47 of the present application. Each of claims 48-55, 57, 59-75,79-82,84-91, 93-96 and 101, ultimately depend from claim 47, and therefore are novel over Landegren at least for the same reasons as claim 47 is novel. As such, Applicants respectfully request that the rejection of claims 47-55, 57, 59-75,79-82,84-91, 93-96 and 101 under 35 U.S.C. §102(b) based on Landegren be withdrawn and the claims be reconsidered for allowance.

V. Rejection under 35 U.S.C. §103(a), should be withdrawn

The remaining claims 56, 58, 76-78, 97 and 99 were rejected under 35 U.S.C. §103 as allegedly being obvious over Landegren in view of Cantor (U.S. Patent No. 5,503,980), claim 92 was rejected under 35 U.S.C. §103 over Landegren in view of Southern (WO 89/10977) and claims 98 and 100 were rejected under 35 U.S.C. §103 over Landegren in view of Duck (U.S. Patent No. 4,876,187). Applicants respectfully traverse these rejections and request reconsideration in view of the present remarks.

Landegren is relied upon as the primary reference for a rejection of each of claims 56, 58, 76-78, 97, and 99; claim 92; and claims 98 and 100 under 35 U.S.C. §103(a) as generally teaching the methods of the invention claimed in the present application. However, as explained above, Applicants respectfully submit that the Examiner is incorrect in his assertions because the Landegren document does not teach a method of sequencing a target nucleic acid as claimed herein but rather is directed to a method of detecting the presence or absence of a point mutation. Moreover, the Landegren method requires that the sequence of the "normal sequence" and the "possible mutation" be known (Col. 2, lines 37-38). In

addition, the Landegren method requires the step of separating the annealed ligated probes from the target nucleic acid. By contrast, the methods of the present invention require neither foreknowledge of the target sequence nor separation of the target sequence from the probes that are used to interrogate the target sequence. As such, Landegren cannot be used to establish a *prima facie* case of obviousness because it fails to teach must teach each element of the claimed invention.

Adding Cantor to Landegren ***does not*** overcome the failings of Landegren. In performing the SBH format 3 method claimed in claim 47 (See discussion above in Section II for art-based recognized definitions of SBH I and SBH 2 as compared with SBH 3 methods of the present invention), it is a requirement that the immobilized and labeled probes that hybridize to the target nucleic acid at positions immediately adjacent to each other are covalently linked to each other (see step (b) of claim 47). The limitations of claim 47 are incorporated into each of dependent claims 56, 58, 76-78, 97 and 99.

In order for Cantor to overcome the failings of Landegren, not only would Cantor have to teach sequencing chips, and/or uracil containing RNA probes and/or fragmentation of the target nucleic acids with restriction enzymes, it would also have to teach the basic method of SBH that Landegren has failed to teach. Applicants submit that Cantor ***does not disclose covalent joining of two probe molecules*** but instead teaches the covalent attachment of a hybridized target nucleic acid molecule to an immobilized oligonucleotide probe. Cantor, which employs one partially double-stranded probe that is attached to a solid support, and that may be ligated to the ***target nucleic acid*** upon hybridization with the target (see Cantor Example 3, column 13, lines 30-35). In addition, Cantor also fails to disclose two sets of probes (*i.e.*, a first set of probes attached to a solid support and the second set of probes which are labeled probes in solution). Thus, much like Landegren, Cantor also fails to disclose the SBH 3 sequencing methods of the present invention.

Thus, regardless of whether or not Cantor provides a teaching of sequencing chips, and/or uracil containing RNA probes and/or fragmentation of the target nucleic acids with restriction enzymes, the basic combination of Landegren with Cantor remains flawed

because it fails to teach SBH format 3 as described above. In the absence of such a teaching, the requirement that every element of the claimed method be taught by the cited art is not met, and therefore a *prima facie* case of obviousness cannot be established.

In light of the above comments, Applicants respectfully submit that claims 56, 58, 76-78, 97 and 99 are non-obvious over the combination of Landegren and Cantor and Applicants request that the rejection be withdrawn.

b. Claim 92 is non-obvious over the Landegren/Southern combination.

Claim 92 is directed to a method of SBH, in which the immobilized probes are immobilized on glass, polystyrene or Teflon. Regardless of the extent of Southern's teachings of immobilized probes on solid surfaces, As explained previously, the Southern document being cited by the Examiner describes SBH format 1, **not SBH 3 as being claimed in the present application**. In SBH 1, the unknown target nucleic acids are labeled and allowed to hybridize to the immobilized oligonucleotides. This is described in Southern at page 2, lines 3-13. Nowhere in Southern is there a technique described in which more than one set of probes (*i.e.*, a first set that is immobilized and a second set that is labeled) is used to determine the sequence of the target nucleic acid. And, as discussed above, Landegren is totally silent on actually determining the nucleotide sequence of the target nucleic acid using SBH, but is instead directed merely to detecting the presence or absence of a point mutation.

Thus, the combination of the two references as cited by the Examiner does not teach a sequencing by hybridization method in which (1) probes from a ***first*** **and** ***second*** set of probes are hybridized to a nucleic acid molecule such that they are adjacent to each other and (2) a hybridized probe from a first set of oligonucleotide probes is covalently bonded to a hybridized probe from a second set of oligonucleotide probes. In the absence of these teachings, the elements of steps (a) and (b) of claim 47 are not met. Thus, regardless of the presence of the teachings in Southern of solid supports for use in SBH format 1, there is still no disclosure of the overall technique of SBH 3. This new and non-obvious method was the

contribution of the instant inventors and was described for the first time in the priority application of the instant application.

In light of the above comments, Applicants respectfully submit that claim 92 is non-obvious over the cited art and that the rejections should be withdrawn.

c. Claims 98 and 100 are non-obvious over the Landegren/Duck combination.

Claims 98 and 100 are respectively directed to the sequencing by hybridization methods of the invention in which the "covalently joined labeled probe comprising ribonucleotides is removed from the immobilized probe by RNAase treatment," (Claim 98) and "covalently joined labeled probe comprising a uracil base is removed from the immobilized probe by uracil-DNA glycosylase treatment." (Claim 100). The Examiner cites U.S. Patent No. 4,876,187 as teaching RNAse and uracil glycolase for washing unhybridized probes and indicated that such treatments may be combined with Landegren's detection methods. However, as Applicants have discussed above, the detection method of Landegren does not teach a method of sequencing the nucleic acid that is being detected. Duck does not rehabilitate Landegren, because Duck is merely directed to specific synthetic molecules that have a scissile bond that is cleaved upon hybridization in order to release the non-hybridized probe. This has nothing to do with sequencing of the target nucleic acid by hydridization with two separate sets of probes, covalently binding those probes that hybridize in positions adjacent to each other and subsequently compiling the sequence of the target nucleic acid. From the disclosure at column 3, lines 1-17 of the Duck patent, it would seem that the synthetic molecule of Duck is one which comprises a label and is designed to hybridize to a nucleic acid molecule of interest. Once the synthetic molecule is hybridized to the molecule of interest, the hybridized complex is immobilized. Subsequently, the scissile bond is cleaved in such a manner as to leave the marker attached/hybridized to the nucleic acid molecule of interest. The presence of the marker on the immobilized nucleic acid molecule of interest facilitates the detection of the nucleic acid molecule. Thus, even if one of skill in the art were to combine both the Duck and Landegren references, the result of that combination would not be a method for sequencing by hybridization but would instead be a

method of detecting a mutation in a nucleic acid (*i.e.*, the method of Landegren) in which method the specific synthetic molecules of Duck may be used to ***label*** the nucleic acid in which the mutation was being detected.

In light of the fact that neither Duck nor Landegren either alone or in combination teach any method of sequencing by hybridization, the mere fact that Duck teaches the use of RNAses and a uracil glycolase is insufficient to render obvious the main SBH methods of the invention, which necessarily are a part of each of claims 98 and 100. Applicants, therefore, respectfully submit that claims 98 and 100 are non-obvious over the cited art and that the rejections articulated by the Examiner at page 8-9 of the Office action should be withdrawn.

VI. Conclusions

Applicants believe that claim 47 (and therefore all of its dependent claims) was readily distinguishable from the methods described by Landegren. Applicants have further clarified the distinction between Landegren and the present methods in the amendment and explanatory comments presented above. Applicants respectfully request that Examiner Siew contact the undersigned representative in the event that further discussion may be required to facilitate allowance of the claims. Applicants respectfully submit that the claims are in condition for allowance and request an early indication of such a favorable disposition of the case.

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Respectfully submitted,

By _____

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